Jeffrey L. Cummings, M.D.

Use of Cholinesterase Inhibitors in Clinical Practice: Evidence-Based Recommendations

Cholinesterase inhibitors (ChE-Is) are the standard of therapy for treatment of patients with Alzheimer disease (AD) and are the only class of drugs approved by the Food and Drug Administration (FDA) for treatment of this condition. This review provides evidenced-based recommendations for use of ChE-Is in clinical practice. The author searched computerized literature databases of the approved ChE-Is widely used in clinical practice (donepezil, rivastigmine, and galantamine), and extended the review with bibliographies from identified articles and package inserts of information reviewed by the FDA. Double-blind, placebo-controlled trials providing Class I evidence were used as data sources whenever possible. Articles with Class II and Class III data were used when Class I data were unavailable. In general, ChE-Is exert modest reproducible effects in patients with mild-to-moderate AD. Drug-placebo differences are evident on global and cognitive measures. Secondary outcomes, including measures of activities of daily living and behavior, also typically demonstrate drug-placebo differences in favor of the active agent. Head-to-head trials of ChE-Is are limited; existing trials suggest no major differences in efficacy. Observations from clinical trials imply that early initiation of therapy is associated with greater long-term benefits. Clinical trials with withdrawal periods indicate that withdrawal and re-initiation of treatment may result in loss of benefit. Open-label extensions of double-blind trials show that differences in level of functioning between treated populations and extrapolated for untreated populations continue for several years. Side effects of ChE-Is include nausea, vomiting, diarrhea, and anorexia, and are more frequent during dose escalation than maintenance therapy. Clinical-trial populations differ substantially from unselected populations of AD patients, and these selection biases demand that efficacy data from clinical trials be generalized with caution.

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Cholinesterase inhibitors (ChE-Is) are increasingly commonly used in the treatment of Alzheimer disease (AD), and evidence-based guidelines recommend ChE-Is as standard therapy for AD (1–4). Despite recommendations for their use, ChE-Is remain a relatively unfamiliar class of agents for many practitioners. The means of initiating therapy, assessing benefit, surveying side effects, and determining the appropriate length of therapy are critical to their successful implementation but have received limited discussion. Four ChE-Is have been approved by the United States Food and Drug Administration (U.S. FDA). Of these, donepezil, rivastigmine, and galantamine are

in common use. In this review, emerging literature on ChE-Is is summarized, and guidelines for ChE-I use based on the available studies are provided.

METHODS

Computerized databases, including MEDLINE and PubMed were searched for literature on the use of ChE-Is in the treatment of AD. Only full-length articles published in Englishwere included. Literature was surveyed to 1993, when tacrine was approved by the FDA for use in AD. Where possible, the critical questions for the clinical use of ChE-Is were addressed using studies providing Class I evidence. Class I evidence is provided by randomized, controlled, clinical trials, including overviews (meta-analyses) of such trials. Class II evidence is derived from well-designed observational studies with concurrent controls (e.g., case-control or cohort studies). Class III evidence is provided by expert opinion, case series, case reports, and studies with historical controls (1). Where Class 1 evidence was unavailable, recommendations were based on Class II or Class III evidence, and this is noted in the text. Package inserts on products marketed in the United States are extensively reviewed by the FDA and contain Class I data regarding effect sizes and side effects not included in published manuscripts; these were used as additional sources of information.

Some important clinical issues (such as when to stop treatment with a ChE-I) have not been studied or reported in the literature. Recommendations are based on pharmacologic principles when no specific empirical data are available. These extrapolations are noted.

TACRINE

Tacrine was the first agent of any class approved specifically for AD therapy. This agent is uniquely associated with substantial hepatotoxicity (5) and has been used little since the introduction of ChE-Is that have comparable efficacy without associated hepatic injury. Data from tacrine studies are cited in this review only when similar data are not available for other agents and the information is useful for recommendations regarding ChE-I use.

CLINICAL PHARMACOLOGY OF CHOLINESTERASE INHIBITORS

The basic clinical pharmacology of ChE-Is is summarized in Table 1. The three ChE-Is approved by the FDA and in widespread clinical use are donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). These three agents represent different classes of ChE-Is and have different pharmacologic properties beyond inhibition of acetylcholinesterase. The half-lives of the three agents differ; donepezil has a longer half-life, and is administered once daily; rivastigmine and galantamine have shorter half-lives, and are administered twice daily. Donepezil and galantamine are metabolized via hepatic cytochrome P450 enzymes; rivastigmine is hydrolized to a phenolic byproduct that is excreted through the kidneys in the urine (6, 7). The average cost of ChE-I treatment is $1,200–$1,800/year.

PRIMARY OUTCOME MEASURES

For approval as an anti-dementia agent, the FDA requires that a significant drug-placebo difference be shown for measures of cognition and global change (8). The Alzheimer's Disease Assessment Scale–Cognitive portion (ADAS–Cog) (9) has typically been used to measure cognitive changes in clinical trials of ChE-Is, and the Clinical Global Impression (CGI) or the Clinical Interview-Based Impression of Change with caregiver input (CIBIC-Plus) (10) have been used to determine the global portion of the dual outcome criteria. The ADAS–Cog is a 70-item tool assessing language, memory, praxis, and visuospatial skills, with higher scores indicating greater impairment. The CIBIC-Plus rates patients on a 7-point scale from showing no change to mild, moderate, or marked improvement or mild, moderate, or marked worsening. Studies performed outside the United States have commonly used translations of these instruments in conjunction with culturally appropriate scales (11).

The drug-placebo difference observed in clinical trials is the difference between the deterioration of the placebo group and the improvement, stabilization, or reduced deterioration in the group receiving the active agent. The magnitude of the difference is related to variations in the rate of decline in the placebo group, as well as any changes induced by the agent.

Table 2 presents the outcomes for the principal controlled studies on the three ChE-Is (results are based on intent-to-treat analyses including all patients receiving at least one dose of drug or placebo). Drug-placebo difference on the ADAS–Cog for 5 mg of donepezil is 2.5 and for 10 mg of donepezil ranges from 2.9 to 3.1 (12–14). Differences on the ADAS–Cog for high-dose rivastigmine (6 mg–12 mg) range from 1.6 to 3.8 (15, 16). Four doses of galantamine have been reported, with drug-placebo differences on the ADAS–Cog ranging from 0.1 to 3.4 points (17–21). Drug-placebo differences on the CIBIC-Plus vary from 0.3 to 0.5 among the clinical trials (Table 2).

Table 1. Clinical Pharmacology of Cholinesterase Inhibitors

Name (Trade Name)	Class	Selectivity	Time to Max Serum Concentration	Food Delays Absorption	Serum Half-Life	Protein Binding (%)	Metabolism	Dose (mg/day)	Daily Dosings
Donepezil (Aricept)	Piperidine	Acetylcholinesterase	3–5 hours	No	70–80 hours	96	CYP2D6, CYP3A4	5–10	1
Rivastigmine (Exelon)	Carbamate	Acetylcholinesterase and butyrylcholinesterase	0.5–2 hours	Yes	2 hours[a]	40	Nonhepatic	6–12	2
Galantamine (Reminyl)	Phenanthrane alkaloid	Acetylcholinesterase; allosteric nicotinic modulator	30–60 minutes	Yes	5–7 hours	10–20	CYP2D6, CYP3A4	16–24	2

a 8-hour half-life for inhibition of brain acetylcholinesterase

No consistent efficacy differences are evident among the ChE-Is on the basis of these measures.

RESPONDERS VS. NON-RESPONDERS

There is no sharp distinction between "responders" and "non-responders" in clinical trials; a spectrum of responses varying from patients who exhibit no improvement to patients changing by 10 or more points on the ADAS–Cog is observed. A standard approach used in package inserts to convey the magnitude of response exhibited by patients included in clinical trials is to determine the number of patients who have at least a 4-point improvement on the ADAS–Cog (equivalent to reversing the disease process by approximately 6 months) (22) and the percentage of patients with at least a 7-point improvement on the ADAS–Cog (equivalent to reversing the disease process by approximately 1 year) (22). Table 3 shows these results for donepezil, rivastigmine, and galantamine. The difference between benefit in the active agent group compared with benefit in the placebo group is approximately 15% across trials of these agents.

RESPONSIVE ITEMS

Responses of individual items on the ADAS–Cog to treatment with ChE-Is have rarely been reported. In a clinical trial of tacrine, patients receiving 80 mg per day performed at significantly higher levels than those receiving placebo on ADAS–Cog items assessing recall, naming, language, and word-finding. No differences were noted for commands, instructions, ideation, orientation, recognition, comprehension, or remembering (23). If these results apply to other ChE-Is, they suggest that aspects of both language and memory contribute to the changes in cognition recorded in clinical trials.

RELATIONSHIP OF RESPONSE TO PHARMACOLOGIC ACTIVITY

Two studies have reported the relationship between drug levels, red blood cell acetylcholinesterase inhibition, and clinical response. Rogers et al. (12) found that doses of 1 mg, 3 mg, and 5 mg of donepezil daily corresponded to serum drug levels of 4.7, 13.1, and 29.6 ng/ml and cholinesterase inhibition levels of 19.4%, 44.3%, and 63.9%. Later studies (13, 14) found that 10 mg produced red cell acetylcholinesterase inhibition of 77.3%. Significant correlation was noted between plasma drug concentrations and changes in ADAS–Cog, Mini-Mental State Exam (MMSE),

Table 2. Comparative Effects of Cholinesterase Inhibitors on Global and Cognitive Outcome Measures (Intent-to-Treat Analyses)

Agent/Study	Duration	CIBIC-Plus[a]		ADAS–Cog[b]	
		Drug/Placebo Difference	Significance (p value)	Drug/Placebo Difference	Significance (p value)
Donepezil					
Rogers et al. (13)	12 weeks				
Placebo					
5 mg		0.3	0.003	2.5	<0.001
10 mg		0.4	0.008	3.1	<0.001
Rogers et al. (14)	24 weeks				
Placebo					
5 mg		0.36	0.005	2.49	<0.001
10 mg		0.44	<0.0001	2.88	<0.001
Rivastigmine					
Corey-Bloom et al. (16)	26 weeks				
Placebo					
1–4 mg		0.29	<0.010	3.78	<0.001
6–12 mg					
Rosler et al. (15)	26 weeks				
Placebo			NS		NS
1–4 mg/day		0.14	NS	0.03	NS
6–12 mg/day		0.47	<0.001	1.6	NS
Galantamine					
Raskind et al. (18)	24 weeks				
Placebo					
24 mg/day		0.28	Sig.[c]	0.1	<0.001
32 mg/day		0.29	Sig.	3.4	<0.001
Tariot et al. (20)	20 weeks				
Placebo					
10 mg/day		0.41	Sig.	3.1	<0.001
24 mg/day		0.44	Sig.	3.1	<0.001
Wilcock et al. (19)	24 weeks				
Placebo					
24 mg/day		0.33	Sig.	2.9	<0.001
32 mg/day		0.47	Sig.	3.1	<0.001

Note: Only studies with complete data are included.
a CIBIC-Plus: Clinician Interview Based Impression of Change with caregiver report
b ADAS–Cog: Alzheimer's Disease Assessment Scale, cognitive portion; higher scores indicate worse performance
c Sig.: Significant difference reported; value not given
NR: not reported
NS: no significant difference

and quality of life (QOL; patient report) scores and between acetylcholinesterase inhibition and change in ADAS–Cog (12). Positron-emission tomographic studies using ligands indicative of cholinergic activity in AD demonstrate that the usual therapeutic doses of donepezil inhibit 27%–40% of brain acetylcholinesterase (24, 25). This suggests that optimal inhibition of central cholinesterase is not achieved by the currently recommended dosing regimen.

SECONDARY OUTCOME MEASURES

A variety of secondary outcome measures have been included in clinical trials of ChE-Is. Measures of activities of daily living (ADL) have been selected for nearly all studies, and some have included assessments of behavior or QOL. These secondary outcomes do not affect regulatory decisions regarding the approvability of ChE-Is in the United States. Patients are not selected or randomized on the basis of secondary outcome measures; differences between placebo and treatment groups may exist at baseline; and definitive response or treatment conclusions cannot be based on these observations. Functioning and behavior, however, are aspects of dementia of great importance to patients, caregivers, and practitioners, and these measures provide preliminary information regarding the effect of ChE-Is on these domains.

Table 3. Percent of Patients With Different Levels of Response to Cholinesterase Inhibitors as Printed on Package Inserts

	ADAS–Cog		
	No Change	At Least 4-Point Improvement	At Least 7-Point Improvement
Donepezil			
30-week study			
Placebo	59%	28%	8%
5 mg/day	83%	40%	15%
10 mg/day	82%	58%	26%
15-week study			
Placebo	72%	30%	14%
5 mg/day	83%	49%	21%
10 mg/day	87%	57%	36%
Rivastigmine			
U.S. 26-week study			
Placebo	26.5%	6.8%	1.6%
1–4 mg	34.5%	11.8%	2.0%
6–12 mg	55.8%	24.8%	11.7%
Global 26-week study			
Placebo	45.3%	18.5%	6%
1–4 mg	48%	16.8%	6.9%
6–12 mg	54.7%	28.6%	17.8%
Galantamine			
U.S. 21-week fixed-dose study			
Placebo	41.8%	19.6%	7.6%
16 mg/day	65.4%	35.6%	15.9%
24 mg/day	64.9%	37.0%	27.3%
U.S. 26-week fixed-dose study			
Placebo	43.9%	16.6%	5.7%
24 mg/day	64.1%	33.6%	18.3%
32 mg/day	58.1%	33.3%	19.7%
International 26-week fixed-dose study			
Placebo	39.8%	15.2%	5.8%
24 mg/day	65.4%	30.8%	15.4%
32 mg/day	63.8%	34.9%	19.7%
International 13-week flexible-dose study			
Placebo	50%	19.4%	5.6%
24 mg or 32 mg	65.3%	22.9%	18.8%

Note: Columns do not add to 100%; those with 7-point change are included in those with at least a 4-point change.
ADAS–Cog: Alzheimer's Disease Assessment Scale, cognitive portion; higher scores indicate worse performance.

ACTIVITIES OF DAILY LIVING

Measures of ADLs include both basic ADLs, such as grooming, toileting, and eating, and instrumental ADLs, such as balancing a checkbook, using public transportation, doing the laundry, or preparing a meal. Some measures used in clinical trials assess both aspects of ADLs, whereas others evaluate only basic or instrumental functions. The Interview for Deterioration in Daily Living Activities in Dementia (IDDD) (26) includes both basic and instrumental ADLs. In a double-blind, placebo-controlled trial of donepezil, those receiving 10 mg per day exhibited significantly less deterioration than patients receiving placebo on measures of instrumental ADLs (27). Mohs and coworkers (28) used the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) to measure ADLs in a randomized trial of 10 mg donepezil versus placebo. Using a survival-type analysis, they showed that donepezil extended the time to clinically measurable decline by 5 months, compared with placebo. At the end of the 1-year trial, 51% of patients on donepezil had not progressed to the predetermined threshold

on ADFACS performance, versus 35% of patients on placebo. The Physical Self-Maintenance Scale (PSMS) (29) was used to measure ADLs in a blinded trial involving treatment with donepezil of AD patients in nursing homes (30). No drug-placebo differences were observed after 24 weeks of therapy. Feldman et al. (31) assessed a group of patients with moderate-to-severe AD (MMSE scores of 5–17) in a double-blind, placebo-controlled trial of donepezil. They included three measures of functioning, including the DAD, instrumental ADL, and PSMS. Significantly greater functional decline was observed in the placebo group compared with the donepezil group on all instruments.

The Progressive Deterioration Scale (PDS) (32) was used to measure the impact of treatment on ADLs in clinical trials of rivastigmine. Corey-Bloom and colleagues (16) showed that high-dose rivastigmine was statistically significantly superior to placebo in both intent-to-treat and observed case (those patients completing the trial) analyses. Rosler et al. (15) found a significant difference in observed cases but not in the intent-to-treat analysis in another trial of rivastigmine using the PDS.

Raskind and colleagues (18) used the Disability Assessment for Dementia (DAD) (33) to determine the efficacy of galantamine in ameliorating the decline of ADLs. At the end of the 6-month double-blind treatment period, there was no significant difference between treatment and placebo groups. Using the same instrument, Wilcock and coworkers (19) noted a drug-placebo difference in favor of galantamine for the patient group receiving 32 mg per day. In a 12-week study, Rockwood and colleagues (17) found a significant difference in DAD scores between patients receiving 24 mg or 32 mg of galantamine and those receiving placebo. Tariot and colleagues (20) used the Alzheimer's Disease Cooperative Study (ADCS) ADL scale (34) in a study of galantamine. Patients on placebo had significantly greater deterioration in ADLs than patients receiving 16 mg or 24 mg of galantamine per day. Wilkinson and coworkers (21) found a difference between galantamine (18 mg, 24 mg, 36 mg/day) and placebo on intent-to-treat analyses.

There has been substantial variability among studies in the outcome assessments used to evaluate ADLs, analyses performed, and the observed result. In the absence of direct comparative trials, it is impossible to deduce whether reported differences relate to differential sensitivity of the measures used, differential efficacy of the agents, or differences in the populations studied. ADLs rarely improve in the course of trials with ChE-Is, and the drug effect is revealed through reduction in the rate of decline compared with patients receiving placebo. Most of these observations are based on secondary analyses; they collectively suggest that ChE-Is slow the rate of functional loss.

BEHAVIOR

Behavioral changes are common in patients with AD; these include apathy, agitation, anxiety, depression, irritability, and delusions (35). The potential behavioral effects of ChE-Is have been examined recently (36). Only one study (30) has been conducted using behavior as a primary outcome; this study found no effect of donepezil on the total Neuropsychiatric Inventory (NPI) (37) score. A post-hoc analysis suggested reduced agitation in the group receiving active agent. In a blinded study using the NPI as a secondary outcome, Feldman and colleagues (31) found that total NPI scores of moderate-to-severe AD patients receiving donepezil improved compared with those receiving placebo. Depression, anxiety, and apathy were the specific symptoms responding to ChE-I therapy. In an open-label trial of patients referred to general practitioners' offices and treated with donepezil, Evans et al. (38) noted that behavioral improvement often occurred in patients without measurable cognition responses to treatment. Tariot and coworkers (20) found that patients receiving 16 mg or 24 mg of galantamine had no change in their total NPI scores during the course of a clinical trial, whereas patients receiving placebo deteriorated behaviorally. Drug-placebo differences at the end of the 5-month trial were statistically significant. Rosler et al. (39) analyzed the behaviors queried on a global assessment scale and reported that patients exhibited stabilization of aggressiveness, hallucinations, and paranoia during a 104-week open-label extension of rivastigmine therapy. Mood disorders also improved during the observation period.

Other studies have found no or limited behavior effects (17, 30) with ChE-Is; responsive items of the NPI have varied among studies; and the effects of ChE-Is on behavior require clarification.

QUALITY OF LIFE

Few studies have attempted to assess quality of life (QOL) in clinical trials of ChE-Is. The methodology for assessing QOL in patients with dementia is in a nascent stage of development, and both the conceptual framework and assessment methodology are evolving. Rogers et al. (12) included a QOL measure with both patient and caregiver versions (40) in a study of donepezil in

AD. No significant difference between drug and placebo was observed, although a dose-trend analysis showed statistically significant improvement across the 1-mg, 3-mg, and 5-mg doses of donepezil. In a subsequent study, a patient-rated 7-point QOL scale was used (14). A statistically significant difference in favor of the 5-mg dose of donepezil was observed at Week 24; there was no drug-placebo difference for the 10-mg dose. QOL instruments that are more responsive to drug-related changes are needed.

DELAY TO NURSING HOME PLACEMENT

Deferring institutionalization of AD patients presents another measure of efficacy of ChE-Is. A post-hoc analysis of the effect of continuing treatment with low-dose tacrine, compared with treatment with high-dose tacrine after termination of the clinical trials of this agent, allowed tentative assessment of the effect on nursing home placement. Those receiving less than 80 mg per day were more likely to have entered a nursing home than those receiving 120 mg or more per day after a minimum follow-up period of 2 years (41). Delay in nursing home placement may be related to reductions in the loss of ADLs or improved behavior, since these influence the decision to institutionalize patients with AD.

PHARMACOECONOMIC OUTCOMES

Pharmacoeconomic outcomes are increasingly viewed as an important measure of the potential impact of drug therapy on healthcare costs. These effects bear importantly on the likelihood of incorporating new therapies into treatment regimens and health maintenance organization (HMO) formularies. Pharmacoeconomic measures, have not been included in clinical trials of ChE-Is. However, economic models of ChE-Is have been constructed to determine whether the beneficial effects would translate into reduced costs or cost trade-offs. Although there is substantial variability in the assumptions and approaches of the available studies, most suggest that if treatment is initiated early and continues for up to 2 years, the cost of ChE-Is will be saved through reductions in other potential costs and delay in nursing home placement (42–49).

MINI-MENTAL STATE EXAM (MMSE)

The MMSE (50) is commonly used to assess mental status of patients with AD. The MMSE, however, has serious limitations as an outcome measure for determining whether ChE-Is are efficacious (51). The MMSE has not been used as a primary outcome measure in any blinded trial of ChE-Is; it has sometimes been used as a secondary outcome. Table 4 presents the results of studies in which data are provided regarding the change in MMSE in clinical trials of ChE-Is. The drug-placebo differences on the MMSE range from 0.68 to 1.36 points. This difference is smaller than the average measurement error of the MMSE of 2.8 points (52) rendering the instrument insensitive to the magnitude of change induced by ChE-Is.

In the absence of an established instrument applicable in clinical practice, the practitioner may conduct a CIBIC-Plus type interview querying the caregiver about change in cognition, functioning, and behavior and directly assessing these with the patient. The MMSE can be a part of this assessment and will reveal changes in patients with large responses.

WHEN TO INITIATE THERAPY

Three studies have made observations relevant to the question of when to begin treatment. Doody and coworkers (53) reviewed data from two double-blind, controlled studies of donepezil that had open-label extensions. In each case, the group maintained on placebo for the first 6 months of the study never evidenced the same degree of cognitive improvement as the group begun on the treatment at the onset of the study. Farlow et al. (54) and Doraiswamy et al. (55) also reported the results of a "delayed start" study with a 6-month delay between initiation of rivastigmine treatment in the active-therapy group and the placebo group. In the open-label continuation, patients with a 6-month delay in initiation of therapy failed to achieve the same cognitive response as those begun at study onset. These differences were statistically significant in both observed care and last-observation-carried-forward (LOCF) analyses (55).

These studies suggest that treatment with ChE-Is should be initiated as early as possible in patients with diagnosed AD. Study populations have been limited to patients with MMSE scores between 10 and 26, and the impact of treatment on patients with more mild disease is unknown.

DURATION OF TREATMENT

Most blinded trials of ChE-Is have been 6 months in duration, although a few have been shorter, and one was 1 year long (Table 2). Thus, double-blind, placebo-controlled data are available for 3–12 months of therapy. Information from open-label extensions are subject to observer bias, but available models suggest that drug-placebo differences are maintained for several years. Rogers and Friedhoff

Table 4. Comparative Effects of Cholinesterase Inhibitors on Mini-Mental State Exam (MMSE) Scores (Intent-to-Treat Analyses)

Agent/Study	Duration	Mean Change From Baseline	Difference	Significance (p value)
Donepezil				
Rogers et al. (12)	12 weeks			
Placebo		1.2		
5 mg/day		2.0	0.8	0.03
Rogers et al. (13)	12 weeks			
Placebo		0.04		
5 mg/day		1.0	0.96	<0.004
10 mg/day		1.3	1.26	<0.001
Rogers et al. (14)	24 weeks			
Placebo		–0.97		
5 mg/day		0.24	1.21	0.0007
10 mg/day		0.39	1.36	0.0002
Rivastigmine				
Rosler et al. (15)	26 weeks			
Placebo		–0.47		
1–4 mg/day		–0.062		
6–12 mg/day		0.21	0.68	<0.05

(56) and Rogers et al. (57) conducted two analyses of the open-label extension of a double-blind, placebo-controlled trial comparing the change in a donepezil-treated group with the anticipated change (based on the annualized rate of deterioration) of the placebo group. They found that changes with prolonged therapy were less than anticipated, compared with the changes predicted for patients without treatment. Studies of similar design but extending over approximately 3 years show a continuing drug benefit, compared with the expected rate of decline for patients not receiving donepezil therapy (57). An open-label observational study compared patients receiving donepezil with a group of patients with a similar baseline MMSE score who were not treated. The patients treated with donepezil declined significantly more slowly over a 1-year period (58).

Farlow and collaborators (54) studied the data from a 6-month, open-label extension of patients included in a 6-month, double-blind, placebo-controlled trial of rivastigmine. This study projected the deterioration observed in the placebo group to investigate differences between patients receiving treatment in the open-label extension and the expected rate of decline based on these projections. Patients continuing to receive rivastigmine functioned at a significantly higher level than that expected for patients without treatment.

These open-label observations suggest that patients receiving continuous treatment with ChE-I for 1 to 3 years continue to function at a higher level than anticipated based on rates of change observed in patients receiving placebo during blinded portions of the studies. Review of prescription data indicate that only 52% of patients who were begun on treatment with donepezil had an adequate 6-month trial of therapy (59). This suggests that considerable patient and physician education is required to achieve the potential benefits of long-term therapy.

INTERRUPTION OF THERAPY

One study has examined the effect of interrupting ChE-I therapy. Doody and colleagues (53) analyzed the results of two double-blind, placebo-controlled trials of donepezil with open-label extensions. In one, a 3-week placebo washout period preceded the initiation of therapy during the open-label extension, and in the other, a 6-week placebo washout period was used. Patients who had undergone shorter periods without treatment functioned at a higher level after re-initiation of therapy. This suggests that any interruption of treatment should be as brief as possible.

The return of patients to the level of functioning of placebo groups after prolonged interruption of therapy in these studies indicates that the effects of ChE-Is are symptomatic and not disease-modifying.

TREATMENT OF PATIENTS WITH MORE ADVANCED AD

Few studies have addressed the efficacy of ChE-Is in improving cognition, functioning, or behavior in patients with more advanced disease. As

noted above, Feldman and colleagues (31) assessed the efficacy of donepezil in patients with MMSE scores between 5 and 17. Significant drug-placebo differences in favor of donepezil were observed on the CIBIC-Plus, MMSE, Neuropsychiatric Inventory (NPI), and Activities of Daily Living (ADL) measures. The Severe Impairment Battery (SIB) (60) also was used to assess cognitive functioning in these more severely impaired patients and showed a significant difference in decline, with greater deterioration in the placebo than in the donepezil-treated patients. Donepezil was studied in a double-blind, controlled trial in AD patients residing in nursing homes (30). The mean age of the patients was 86 years, and the mean MMSE score was 14. Assessments were made at Weeks 4, 8, 12, 16, 20, and 24; drug-placebo differences in cognitive measures (MMSE) were evident at Weeks 8, 16, and 20. The Clinical Dementia Rating (CDR) scale (61) favored donepezil at Week 24. No drug-placebo differences were obtained for the PSMS or the total score of the NPI–Nursing Home version (NPI–NH) (62). As noted above, one NPI–NH item, aggression, improved more with donepezil than placebo. The available data tentatively suggest that these agents may be beneficial to patients with more severe dementia.

RESPONSIVE SUBPOPULATIONS

A critical clinical issue is whether some patients are more responsive than others to ChE-Is and whether these patients can be identified prospectively. Relatively few studies have systematically addressed this question. Wilcock and colleagues (19) observed that patients with MMSE scores lower than 18 had a more robust response to galantamine than patients with MMSE scores of 18 or higher. Similarly, patients with MMSE scores of 20 or below had larger responses to donepezil than those with scores above 20 (63). These differences may represent instrument properties or true differences in treatment responsiveness. Using ADLs as the outcome measure, Potkin and colleagues (64) showed that patients with moderate-to-severe AD had more robust responses than patients with mild AD treated with rivastigmine. Kim et al. (65) also found that lower scores on ADL scales predicted efficacy of ChE-I therapy among Korean patients with AD. Farlow and collaborators (66) examined data from a double-blind, placebo-controlled trial of rivastigmine with an open-label extension period. They reported that patients who declined more rapidly during the blinded phase had a larger response to treatment with rivastigmine than patients who declined more slowly. Mega et al. (35) analyzed behavioral responses to treatment with donepezil as assessed by the NPI in patients receiving open-label therapy. They found that patients with more severe behavioral deficits exhibited significantly greater responses to donepezil therapy. Kumar and coworkers (67) conducted a post-hoc analysis of a double-blind, placebo-controlled trial of rivastigmine and found that patients with more vascular risk factors had a significantly larger response than those without such risk factors. Patients with the ε4 allele of the apolipoprotein gene (ApoE ε4) were found to be less responsive to tacrine treatment than those without the ε4 genotype (68); no effect of ApoE genotype on response to galantamine (69) or donepezil (70) was found. One openlabel study of patients referred to general practitioners' offices found that patients under age 65 had a significantly larger response to treatment with donepezil than those over age 65 (38).

Thus, post-hoc analyses suggest that patients with more severe disease, as manifested by greater cognitive impairment, more severe disability, more rapid rate of decline, greater comorbidity, or more associated psychopathology, appear to have larger responses to ChE-I therapy. Given the variability of these responses and the lack of definitive response predictors, ChE-Is should be considered for all patients with AD of mild-to-moderate severity (1, 2).

SIDE EFFECTS

Gastrointestinal side effects are the most common adverse events observed in clinical trials of ChE-Is, and they are common. It is difficult to compare the rate of adverse events across clinical trials because rates vary among different populations (including patients receiving placebo), with different adverse-event assessment strategies, and with differing treatment strategies. Maximum-tolerated-dose approaches used in clinical trials of rivastigmine may have contributed to the greater frequency of side effects than reported with donepezil and galantamine. Table 5 shows the percent of patients completing trials of donepezil, rivastigmine, and galantamine, showing both percent withdrawn because of adverse effect and the percent experiencing side effects in the course of the trial.

Table 6 presents side effects included in the package insert that were reported to occur at a higher rate than placebo and in at least 2% of patients receiving the active agents. Nausea is the most commonly reported adverse event (11%–47%); vomiting, the next most common (10%–31%); diarrhea, next in order of frequency (5%–19%); and anorexia, the least common (reported in 4%–17%).

Table 5. Comparison of Adverse Events Reported in Clinical Trials of Cholinesterase Inhibitors (Only Studies With Complete Data Included)

Agent/Study	% Not Completing	% Withdrawn Due to Adverse Effects	% With Side Effects
Donepezil			
Rogers et al. (13)			
Placebo	7	1	69
5 mg/day	10	4	68
10 mg/day	18	9	78
Burns et al. (27)			
Placebo	20	10	76
5 mg/day	22	9	79
10 mg/day	26	18	86
Rivastigmine[a]			
Rosler et al. (15)			
Placebo	13	7	72
1–4 mg/day	14	7	71
6–12 mg/day	33	23	91
Galantamine			
Raskind et al. (18)			
Placebo	29	8	79
24 mg/day	32	23	92
32 mg/day	42	32	92
Tariot et al. (20)			
Placebo	16	7	72
16 mg/day	22	7	74
24 mg/day	22	10	80
Wilcock et al. (19)			
Placebo	13	9	77
24 mg/day	20	14	83
32 mg/day	25	22	89
Rockwood et al. (17)			
Placebo	11	4	63
24 mg/day	49	38	86
Wilkinson et al. (21)			
Placebo	16	9	44
18 mg/day	29	22	56
24 mg/day	25	18	59
36 mg/day	48	44	70

a Forced titration at 1-week intervals of rivastigmine may have increased side effect rates compared with slower titration schedules.

The package insert for rivastigmine instructs clinicians to monitor patients for vomiting and weight loss when using this agent. Other adverse events occurring more commonly with ChE-Is than placebo include insomnia, abnormal dreams, incontinence, muscle cramps, bradycardia, syncope, and fatigue. ChE-Is are relatively contraindicated in patients with bradycardia, sick-sinus syndrome, active peptic ulcer disease, or severe asthma.

Information included in package inserts demonstrates that a slower rate of dose escalation is associated with the emergence of fewer adverse events. Patients achieving a maintenance dose also experience fewer side effects than reported during drug introduction and dose escalation. A head-to-head comparison of donepezil and rivastigmine using a 4-week titration strategy for donepezil and a 1-week titration with the rivastigmine group found more side effects in those receiving rivastigmine (71). Observations from non-research clinical practices in Austria similarly demonstrated that rivastigmine is best titrated more slowly than recommended in the package insert (72).

Predictors of adverse events have received little study. Kim et al. (65), in an open-label study of patients receiving either donepezil or rivastigmine, found that the presence of depression or anxiety and treatment with psychotropic agents correlated with adverse-event frequency.

SWITCHING AMONG CHOLINESTERASE INHIBITORS

The availability of multiple ChE-Is presents the practitioner with the option of switching from one to another. Co-administration of two ChE-Is has not been studied and is not recommended. Two studies had addressed switching from donepezil to rivastigmine. In an open-label study of patients who were intolerant of donepezil or who declined cognitively or functionally despite donepezil therapy, 56% experienced improvement or stabilization on a global measure and 50% evidenced a 1-point improvement or stabilization on the MMSE with rivastigmine (73). Poor tolerability with donepezil did not predict poor tolerability to rivastigmine. Similarly, in a survey of practitioners in British memory clinics, Bullock and Connolly (74) found that 55% of patients switched from donepezil to rivastigmine were reported to have improved. A post-hoc analysis found that patients switched to galantamine from another ChE-I had the same average magnitude of response as patients without previous ChE-I treatment (75). No Class I evidence is available on switching effects and adverse events.

The optimal procedure of switching from one ChE-I to another is controversial. Zero- to 7-day drug-free periods have been suggested when switching from donepezil (76), but several experts have recommended switching with no interruption of therapy (77–79). This recommendation, however, has been contested, since it represents co-administration of two ChE-Is. Given the long half-life of donepezil; additive toxicity is possible (80). A conservative strategy suggests that when switching from one agent to another, cessation of therapy for five half-lives using the terminated agent will minimize the opportunities for adverse drug interactions. Thus, patients should be off donepezil for 15 days and off rivastigmine or galantamine for 2 days before initiating therapy with the subsequent ChE-I.

Indications for switching include allergic responses, unmanageable side effects, family preference, and unmitigated cognitive decline after at least a 6-month trial of treatment.

USE OF CHE-IS IN NON-ALZHEIMER DEMENTIAS

ChE-Is have been studied to only a limited extent in non-AD dementias. A double-blind study of rivastigmine in dementia with Lewy bodies found significant drug-placebo differences in favor of rivastigmine on the NPI and computerized measures of cognition (81). Similarly, a randomized, controlled trial of galantamine showed this agent to be superior to placebo in the treatment of vascular dementia and in AD with cerebrovascular disease (82). An open-label study observed behavioral benefits in response to treatment with rivastigmine in patients with Parkinson disease, dementia, and hallucinations (83). A blinded study showed no donepezil-placebo differences in patients with progressive supranuclear palsy (84). and an open-label study found no effect of donepezil on patients with Huntington disease (85). These observations suggest that patients with presynaptic cholinergic deficits may be appropriate ChE-I treatment candidates.

Table 6. Percent of Patients With Gastrointestinal and Selected Other Side Effects as Presented in the Package Insert for Each Agent

Event	Donepezil/ Placebo	Rivastigmine/ Placebo	Galantamine/ Placebo
Nausea	11/6	47/12	24/9
Vomiting	10/5	31/6	13/4
Diarrhea	5/3	19/11	9/7
Weight decrease	3/1	3/1	7/2
Insomnia	9/6	9/7	5/4
Abnormal dreams	3/0	NA	NA
Muscle cramps	6/2	NA	NA
Bradycardia	NA	NA	2/1
Syncope	2/1	3/2	2/1
Fatigue	5/3	9/5	5/3

Note: NA: not applicable; event did not occur at a rate higher than placebo and in at least 2% of patients receiving the active agent

CLINICAL TRIAL POPULATIONS ARE NOT REPRESENTATIVE OF COMMUNITY-DWELLING PATIENTS

Individuals participating in clinical trials are not representative of an unselected clinical population of patients with AD. Patients participating in clin-

Table 7. Ethnic Composition of Clinical Trial Populations

	White	Black	Other
Rogers et al. (12)	115 (95%)	5 (4%)	1 (0.8%)
Rogers et al. (13)	448 (96%)	13 (3%)	7 (0.2%)
Rogers et al. (14)	449 (95%)	14 (3%)	10 (2%)
Burns et al. (27)	813 (99%)	NR	5 (1%)
Corey-Bloom et al. (16)	668 (97%)	15 (2%)	6 (1%)
Rosler et al. (15)	703 (97%)	NR	22 (3%)
Raskind et al. (18)	581 (91%)	NR	55 (8%)
Tariot et al. (20)	908 (93%)	NR	70 (7%)

Note: NR: not separately reported; all non-whites reported collectively

ical trials tend to be better educated, wealthier, and younger than patients in similar clinical circumstances not enrolled in trials (86, 87). They have fewer physical illnesses and are less behaviorally disturbed than patients not enrolled. They deteriorate more slowly and experience lower mortality rates than non-participants. Schneider and coworkers (87) examined eligibility criteria for two clinical trials with typical inclusion and exclusion criteria and found that only 4.4% or 7.9%, respectively, of patients with AD included in a large clinical database would have been eligible for the two trials.

Few minority patients are included in clinical trials, and the overwhelming majority of patients for whom data are available are white. Table 7 shows the ethnicity of patients enrolled in eight clinical trials in which the ethnic composition of the trial population was reported. From 91% to 99% of patients included in the trials were white.

Care for patients in clinical trials is delivered in circumstances that differ substantially from community clinics. Care is rendered in academic medical centers or clinical-trial organizations. Clinicians conducting clinical trials are very familiar with the management of AD and are highly motivated to ensure that patients maintain participation throughout the trial. Thus, both trial participants and trial circumstances are unlike those of routine clinical practice settings, and results of clinical trials should be generalized with caution.

CONCLUSION

Discovery of the cholinergic deficit in AD ushered in new phase in the treatment of AD with ChE-Is. Recent advances in understanding the genetics and molecular biology of AD suggest that new therapeutic interventions that ameliorate amyloid accumulation, reduce inflammatory responses, limit oxidative injury, or exert other neuroprotective effects will likely emerge in the foreseeable future. These drugs are anticipated to have their greatest effect on the prevention of AD or slowing of its progression. We expect to see continued use of ChE-Is in combination with these agents for patients with established AD.

The effects of ChE-Is are modest in extent and are multidimensional, involving cognition and functioning. Secondary effects on behavior, QOL, time to nursing home placement, and healthcare costs are suggested by some studies. Assessment of the response to ChE-Is should include information from both the patient and the caregiver pertaining to alterations in ADLs, behavior, and cognition.

The evidence base for use of ChE-Is is growing, but it currently emphasizes efficacy and tolerability. Areas that require additional study to inform optimal use of these components include addressing how long to use them, how best to gauge response, how to minimize side effects, whether there are meaningful response differences among ChE-Is, how best to switch from one agent to another, and whether higher doses would enhance efficacy.

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